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Jc600 U.S. PTO

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Assistant Commissioner for Patents  
Washington, D.C. 20231

*A*  
Date: July 27, 1999  
35615.1

Sir:

Enclosed herewith for filing are the specification, claims and abstract of the patent application of:

Inventor(s): [List all names] Philippe **MAINGAULT**, Edit **DELLACHERIE**, Patrick **HUBERT**, Marie-Christine **HOUZELLE** and Sophie **PELLETIER**

For: **SYSTEM FOR TREATING WOUNDS AND METHOD FOR PRODUCING THIS SYSTEM**

☒ Also enclosed are:

☐ Executed declaration or oath.

☒ 2 sheets of drawings

☐ A Recordation Form Cover Sheet and an assignment of the invention (\$40.00 check enclosed)

☒ A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27

☒ Our check in the amount of \$380.00 is enclosed to cover:

☒ the filing fee of \$380.00; (check is enclosed)

☒ Information Disclosure Statement under Rule 98;

☒ Submission Of Priority Document

☒ Other: Certified French Application No. 98 09858 filed July 31, 1998.

☒ The benefit of priority under 35 USC 119 is hereby claimed from the following foreign application(s): French Application No. 98 09858 Filed July 31, 1998.

☐ The benefit of priority under 35 USC 120 is hereby claimed from the following United States application(s)

☒ The Commissioner is hereby authorized to charge any deficiency in the basic filing fee associated with this communication under 37 CFR §1.16(a) only to our Deposit Account No. 07-1855. A duplicate copy of this sheet is enclosed.

**Do not charge our Deposit Account for any deficiency in any fee for multiple dependent claims and/or excess claims.**

**"EXPRESS MAIL** Tracking label No. FM047497543US  
Date of Deposit July 27, 1999  
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Service "Express Mail Post Office to  
Addressee" service under 37 CFR 1.10 on the  
date indicated above and is addressed to the Assistant  
Commissioner of Patents, Washington, DC 20231.

*Julian Meaia*

Respectfully Submitted,

By: **GRAHAM & JAMES LLP**  
*Eugene C. Rzuca*  
Per: Eugene C. Rzuca  
Reg. No. 31,900

Jc530 U.S. PTO  
09/364908  
07/27/99

**VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS  
(37 CFR 1.9(d) & 1.27(c))--SMALL BUSINESS CONCERN**Docket Number (Optional)  
35615.1Applicant or Patentee: Philippe MAINGAULT et al

Serial or Patent No.: \_\_\_\_\_

Filed or Issued: \_\_\_\_\_

Title: SYSTEM FOR TREATING WOUNDS AND METHOD FOR PRODUCING THIS SYSTEM

I hereby declare that I am

- ☐ the owner of the small business concern identified below;  
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN LES LABORATOIRES BROTHIERADDRESS OF SMALL BUSINESS CONCERN 41 rue de Neuilly, 92000 Nanterre, France

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

- ☒ the specification filed herewith with title as listed above,  
☒ the application identified above,  
☐ the patent identified above.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention must file separate verified statements averring to their status as small entities, and no rights to the invention are held by any person other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization having any rights in the invention is listed below:

- ☒ no such person, concern, or organization exists.  
☐ each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. 37 CFR 1.27

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Christian GIRARDIERETITLE OF PERSON IF OTHER THAN OWNER Chairman of the BoardADDRESS OF PERSON SIGNING 41 rue de Neuilly, 92000 Nanterre, FranceSIGNATURE [Signature] DATE July 22, 1999

PTO/SB/10 (11-90)

Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

09364008 072799 662220 80549660

## **SYSTEM FOR TREATING WOUNDS AND METHOD FOR PRODUCING THIS SYSTEM**

The invention relates to a treatment product or system intended for the care of patches of necrosis, acute surgical wounds and other types of wounds.

Two types of wound-treatment products will mainly be considered.

The products of the first type are natural products and include polysaccharide molecules. They are, for example, alginate-based products. The products of this type have intrinsic natural properties which are highly effective in treating wounds.

The products of the second type are synthetic and for this reason have less effective curative properties.

The treatment products, whether natural or synthetic, are generally used as a solution or as a gel.

In the solution state the treatment product is easily applied and distributed over the wound and comes into close contact therewith. However, the distribution of the solution is generally not uniform and the solution inevitably runs out of the wound even with a protective, sealing dressing.

In the gel state the treatment product can certainly be held more easily on the wound by a dressing but does not come into close contact with it.

Reversible synthetic treatment gels are also known. These gels are known as "reversible" by reason of the fact that they can change state in a reversible manner by passing from the gel state to the solution state and vice-versa. This gel/solution reversibility is made possible by synthetic macromolecules forming the product, which have intrinsically reversible configurations.

Table 1. Demographic characteristics of the study population	
Age (years)	Mean (SD)
Male	55.2 (10.5)
Female	56.8 (11.2)
Marital status	
Married	78.5%
Single	21.5%
Education level	
High school or above	65.2%
Below high school	34.8%
Occupation	
Professional	12.3%
Managerial	18.7%
Technical	25.4%
Service	32.1%
Unemployed	11.5%
Income (USD/month)	
< 1000	15.6%
1000-2000	28.9%
2000-3000	35.2%
> 3000	20.3%
Health insurance	
Yes	89.1%
No	10.9%
Smoking status	
Smoker	22.4%
Non-smoker	77.6%
Alcohol consumption	
Regular	8.7%
Occasional	14.3%
Never	77.0%
Comorbidities	
Hypertension	35.2%
Diabetes	18.7%
Cholesterol	25.4%
Obesity	12.3%
Depression	10.5%
Family history of cancer	
Yes	15.6%
No	84.4%

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Cholesterol	25.4%
Obesity	12.3%
Depression	10.5%
Medication use	
Antidepressants	15.2%
Antipsychotics	8.7%
Mood stabilizers	12.3%
Other psychotropic drugs	18.9%
Non-psychotropic drugs	44.9%

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Mood stabilizers	12.3%
Other psychotropic drugs	18.9%
Non-psychotropic drugs	44.9%

The treatment products having aliphatic chains with twenty carbon atoms are indicated for the treatment of chronic wounds in the epidermization phase.

For an acute surgical type wound, for example, the treatment products having aliphatic chains with sixteen carbon atoms and/or aliphatic chains with twelve carbon atoms are particularly indicated because they have biological and bio-adhesion properties making it possible to reduce tissue adherence at interfaces.

Of course, it is possible to attach aliphatic chains of different lengths to polysaccharide macromolecules in order to obtain a product with multiple properties and to increase the efficacy of the product still further.

It will be noted at this point that the document EP-0 341 745 discloses a product obtained by chemical cross-linking, having polysaccharide macromolecules linked to each other by transverse bonds or "cross-linking bridges" consisting of aliphatic chains. Each of these aliphatic chains links two polysaccharide macromolecules by high-energy chemical bonds. This results in the product being in the solid state, or the gel state, and being irreversible.

The aliphatic chains are advantageously attached by a chemical bond.

The said chemical bond can be an ionic bond or a covalent bond, for example, an ester bond.

It is also advantageous for the aliphatic chains attached to a polysaccharide macromolecule to be associated - in the gel state - with aliphatic chains attached to at least one other polysaccharide macromolecule.

The aliphatic chains thus constitute hydrocarbonic arms by means of which the macromolecules are associated with each other.

The invention also relates to a method for producing the wound-treatment system discussed above, during which polysaccharide macromolecules and aliphatic chains each provided with a

single attachment group are used and the said polysaccharide macromolecules and the said aliphatic chains are brought into contact so as to attach the aliphatic chains to the macromolecules.

The invention also relates to a natural wound-treatment system such as that defined above, wherein molecules of an active principle are trapped in alveoli of the system in the gel state.

The invention finally relates to a natural wound-treatment system such as that defined above, wherein the living cells are trapped in alveoli of the system in the gel state.

The invention will be better understood with the aid of the following description of different embodiments of the wound-treatment system and of different embodiments of the method for producing the treatment system, with reference to the attached drawing in which:

- Figure 1 illustrates three macromolecules of the treatment system in the gel state, according to one particular embodiment;
- Figure 2 illustrates stages of the method for producing the treatment system according to one of the embodiments;
- Figure 3 illustrates the treatment system in which molecules of an active principle are trapped before the active principle is released.
- Figure 4 illustrates the treatment system of Figure 3 during the release of the active principle;
- Figure 5 illustrates the treatment system in which living cells are trapped before these cells are released, and
- Figure 6 illustrates the treatment system of Figure 5 during release of the cells.

The wound-treatment system or product comprises polysaccharide macromolecules, 10, 20,

30, in this case alginate macromolecules, and aliphatic chains 11-15, 21-24, 31-33, in this case of the formula  $C_nH_{2n+1}$ . The number of carbon atoms of the aliphatic chains is in this case 8.

In the particular example of the description each aliphatic chain 11-15, 21-24, 31-33 is provided with a single attachment group, in this case an ionised amine group  $NH_3^+$ , by means of which it is attached to a single alginate macromolecule 10, 20, 30 by a chemical bond consisting of an ionic bond between the ionised amine group  $NH_3^+$  and an ionised carboxylate group  $COO^-$  of the alginate macromolecule.

The aliphatic chains 11-15, 21-24, 31-33 of each macromolecule 10, 20, 30 form hydrocarbonic arms which - when the system is in the gel state - are associated with hydrocarbonic arms of at least one other neighbouring macromolecule. In Figure 1 it is possible to see that the hydrocarbonic arms of each of the macromolecules 10 (20; 30) are associated with hydrocarbonic arms of the two other macromolecules 20, 30 (10, 30; 10, 20). Each association of hydrocarbonic arms has a number  $m$  of hydrocarbonic arms,  $m$  being a natural number greater than or equal to two. The hydrocarbonic arms 11/21, 12/22/13, 14/32/15/33, 23/31/24 of each association of arms are linked to each other by physical bonds consisting of hydrophobic interactions. The alginate macromolecules 10, 20, 30 are thus associated with each other by means of their hydrocarbonic arms 11-15, 21-24, 31-33.

The hydrophobic interactions between the associated arms 11/21, 12/22/13, 14/32/15/33, 23/31/24 of the macromolecules 10, 20, 30 have an energy which is both sufficiently great to ensure sufficient strength for the system in the gel state, and sufficiently weak to permit this gel to pass into the solution state under the effect of external forces such as the temperature, mechanical forces, pH, ionic strength, etc. Moreover, this change of state is reversible. In other words, under the effect of external forces, the system can pass from the gel state to the solution state by separation of the associated hydrocarbonic arms 11/21, 12/22/13, 14/32/15/33, 23/31/24 and, conversely, from the solution state to the gel state by association of the hydrocarbonic arms 11-15, 21-24, 31-33.

In this way it is possible, in particular, to pour the alginate system in the solution state onto the wound to be treated so that it conforms to the shape of the wound and comes into close contact with it. After a setting time the system gels and so adheres closely to the wound without the risk of running. Then under the effect of the ionic strength of the biological tissue medium and/or of the pH thereof, the alginate gel located in the proximity of the wound liquefies so that in spite of possible mechanical forces (changes in the wound, movement of the patient) the close contact between the treatment system and the wound will always be maintained.

It would also be possible to attach aliphatic chains to the polysaccharide macromolecules, which aliphatic chains have six, seven or more than eight carbon atoms, in order to obtain a reversible treatment system.

Moreover, one and the same wound-treatment system could have aliphatic chains of different lengths.

In one variation, the aliphatic chains are attached by covalent bonds, in this case ester bonds, as will be explained hereinafter.

Having described the treatment system of the invention, the method for producing this system according to two embodiments will now be described. These two embodiments are the following:

- 1) attachment of aliphatic chains by covalent bond to alginate macromolecules and
- 2) attachment of aliphatic chains by ionic bond to alginate macromolecules.

1) Attachment of aliphatic chains by covalent bond to alginate macromolecules

With reference to Figure 2 an aqueous suspension of alginic acid is used at a level of 2% by weight. The suspension includes macromolecules of alginic acid 40 each having a plurality of functional carboxylic groups. These functional groups include, for the most part, a carboxylic group COOH, and in a small proportion of them, a carboxylate group COO<sup>-</sup> linked to a



sodium ion  $\text{Na}^+$ .

The suspension is neutralised by tetrabutyl ammonium hydroxide ( $\text{TBA}^+\text{OH}^-$ ) so that the pH is 7. The tetrabutyl ammonium groups  $\text{TBA}^+$  are substituted for protons of hydrogen  $\text{H}^+$  in the functional carboxylic groups of the macromolecules of alginic acid 40. The polysaccharide macromolecules 41 thus obtained are those of an ammonium derivative of the alginate including highly reactive functional carboxylic groups ( $\text{COO}^-\text{TBA}^+$ ).

Then, over a period of 24 hours, the macromolecules 41 are placed in a solvent medium, in this case dimethyl sulfoxide DMSO, in the presence of molecules 44 of an aliphatic brominated derivative of the formula  $\text{C}_n\text{H}_{2n+1}\text{Br}$ . The number  $n$  of carbon atoms of the molecules 44 is twelve. Each molecule 44 has an aliphatic chain (of the formula  $\text{C}_n\text{H}_{2n+1}$ ) and a bromine atom ( $\text{Br}$ ) forming a single attachment group of the aliphatic chain. Thus the polysaccharide macromolecules 41 are brought into contact with the aliphatic chains 44.

The molecules 44 of the aliphatic brominated derivative react on the macromolecules 41 of the alginate ammonium derivative. Aliphatic chains  $\text{C}_n\text{H}_{2n+1}$  are substituted for the tetrabutyl ammonium groups  $\text{TBA}^+$  of some of the functional groups of the macromolecules 41 of the alginate derivative, losing their bromine atom. The level of substitution is of the order of 8%. Thus aliphatic chains  $\text{C}_n\text{H}_{2n+1}$  are attached to the alginate macromolecules. Each of these attached aliphatic chains is linked to a carboxylate group ( $\text{COO}^-$ ) by a covalent bond, in this case an ester bond. The aliphatic chains are each attached to a single alginate macromolecule. The macromolecules 42 shown in Figure 2 are obtained.

Finally the solution is dialysed in the presence of sodium azide ( $\text{NaN}_3$ ) so as to substitute the remaining tetrabutyl ammonium groups  $\text{TBA}^+$  of the macromolecules 42 with sodium ions  $\text{Na}^+$ , thus losing the ammonium functionality.

The final reversible alginate system to be used for wound treatment is obtained, including alginate macromolecules 43, illustrated in Figure 2, each having about 92% of functional sodium carboxylate groups (of formula  $\text{COO}^-\text{Na}^+$ ) and 8% of functional groups esterified by

aliphatic chains with twelve carbon atoms (of formula  $\text{COO-C}_n\text{H}_{2n+1}$ ).

## 2) Attachment of aliphatic chains by an ionic bond to alginate macromolecules

Two grammes of sodium alginate are used and placed in suspension in a water-alcohol solution, in this case 140 millilitres of ethanol at 90%.

Molecules of aliphatic amine of the formula  $\text{C}_n\text{H}_{2n+1}\text{NH}_2$  are added to the solution. The number  $n$  of carbon atoms of the aliphatic amine molecules is in this case 12. Each aliphatic amine molecule has an aliphatic chain (of formula  $\text{C}_n\text{H}_{2n+1}$ ) and a single amine group (of formula  $\text{NH}_2$ ) constituting an attachment group for the aliphatic chain. In solution the amine groups of the aliphatic amine molecules ionise by capturing a proton. Thus the attachment groups of the aliphatic chains are activated by ionisation. Each aliphatic amine molecule thus has a single active attachment group of the formula  $\text{NH}_3^+$ .

In the solution the alginate macromolecules are in contact with the ionised aliphatic amine molecules.

The solution is agitated at ambient temperature for 90 minutes. During this time the ionised aliphatic amine molecules ( $\text{C}_n\text{H}_{2n+1}\text{NH}_3^+$ ) react on the alginate macromolecules and are substituted for the protons of some carboxylic functional groups of the alginate macromolecules. Thus aliphatic chains are attached to the alginate macromolecules by means of their active attachment group  $\text{NH}_3^+$ . The attached aliphatic chains are each linked to a single alginate macromolecule by means of an ionic bond between the attachment group ( $\text{NH}_3^+$ ) and a carboxylate group ( $\text{COO}^-$ ) of the alginate macromolecule.

The alginate macromolecules thus obtained therefore have carboxylate groups ( $\text{COO}^-$ ) some of which are linked to a sodium atom ( $\text{Na}^+$ ) by an ionic bond, and some of which are linked to an aliphatic chain ( $\text{C}_n\text{H}_{2n+1}$ ) by means of an attachment group ( $\text{NH}_3^+$ ) by an ionic bond.

Washing is then carried out several times in an ethanol solution, then in a dioxane solution and

finally in an acetone solution in order to obtain a dry modified alginate which will provide a reversible alginate gel after dissolution in water.

The use of the treatment system described above for release of an active principle will now be described.

In the treatment system in the gel state (Figure 3) the alginate macromolecules 51-53 are associated with each other by means of their mutually associated hydrocarbonic arms. By reason of these associations between macromolecules, the gel structure at the macromolecular level is alveolar, the walls of the alveoli being formed by mutually associated hydrocarbonic arms and by skeletal portions of the alginate macromolecule. The alveoli 54-55, or reservoirs, of the system act as traps for other molecules.

In Figure 3, molecules 60 of an active principle, which are intended to be released at their application site, in other words on the wound to be treated 100, are trapped inside alveoli 54-55.

The molecules 60 of the active principle have been introduced into the treatment system in the solution state. After a setting period in suitable conditions the solution is gelled, trapping the molecules 60 of the active principle in the alveoli 54-55 of the gel.

The treatment gel containing the molecules 60 of the active principle applied to the wound liquefies in the immediate proximity of the skin under the effect of external forces such as body temperature and the ionic strength of the medium. Upon liquefaction the associated arms separate from each other. This means that the alveoli 54-55 open, releasing the molecules 60 of the active principle onto the wound 100.

In one variation (Figure 4), in place of the active principle, living cells 70, animal or vegetable, are trapped in the alveoli 71, 72 of the reversible treatment gel. These may, for example, be cells intended to re-form damaged cartilage.

In this case the opening of the alveoli 71, 72 for release of the cells 70 could be induced by external forces similar to those discussed above (body temperature, ionic strength, mechanical forces, etc) and/or by internal forces caused by growth of the trapped cells.

## CLAIMS

1. Natural wound-treatment system, adapted to change state in a reversible manner by passing from the gel state to the solution state and vice-versa, having polysaccharide macromolecules (10, 20, 30) and aliphatic chains (11-15, 21-24, 31-33) attached to a single polysaccharide macromolecule.
2. System according to claim 1, wherein the aliphatic chains (11-15, 21-24, 31-33) are attached by a chemical bond.
3. System according to claim 2, wherein the said chemical bond is an ionic bond.
4. System according to claim 2, wherein the said chemical bond is a covalent bond.
5. System according to claim 4, wherein the chemical bond is an ester bond.
6. System according to claim 1, wherein each aliphatic chain is attached by means of an attachment group.
7. System according to claim 1, wherein the aliphatic chains (21-24) attached to a polysaccharide macromolecule (20) are, in the gel state, associated with aliphatic chains (11, 12/13, 31) attached to at least one other polysaccharide macromolecule (10, 30).
8. System according to claim 7, wherein the associated aliphatic chains (11/21, 12/22/13, 14/32/15/33, 23/31/24) are linked to each other by a physical bond.
9. System according to claim 1, wherein the aliphatic chains (11-15, 21-24, 31-33) have at least six carbon atoms.
10. System according to claim 1, wherein the polysaccharide is an alginate.

11. Method for producing the wound-treatment system of claim 1, during which polysaccharide macromolecules (41) and aliphatic chains (44) each provided with a single attachment group are used and the said polysaccharide macromolecules (41) and the said aliphatic chains (44) are brought into contact so as to attach aliphatic chains (44) to the macromolecules (41).

12. Method according to claim 11, wherein the attachment group of the aliphatic chains is activated by ionisation.

13. Method according to claim 12, wherein the aliphatic chains provided with an attachment group are molecules of aliphatic amine.

14. Method according to claim 11, wherein the molecules of polysaccharide and the aliphatic chains provided with an attachment group are placed in a water-alcohol solution.

15. Natural wound-treatment system according to claim 1, wherein the molecules (60) of an active principle are trapped in alveoli (54, 55) of the system in the gel state.

16. Natural wound-treatment system according to claim 1, wherein living cells (70) are trapped in alveoli (71, 72) of the system in the gel state.

## ABSTRACT

### SYSTEM FOR TREATING WOUNDS AND METHOD FOR PRODUCING THIS SYSTEM

The wound-treatment system is natural and is adapted to change state in a reversible manner by passing from the gel state to the solution state and vice-versa, and has polysaccharide macromolecules (10, 20, 30) and aliphatic chains (11-15, 21-24, 31-33) attached to a single polysaccharide macromolecule. The aliphatic chains (21-24) attached to a polysaccharide macromolecule (20) are, in the gel state, associated with aliphatic chains (11, 12/13, 31) attached to at least one other polysaccharide macromolecule (10, 30) by physical bonds.

Figure 1

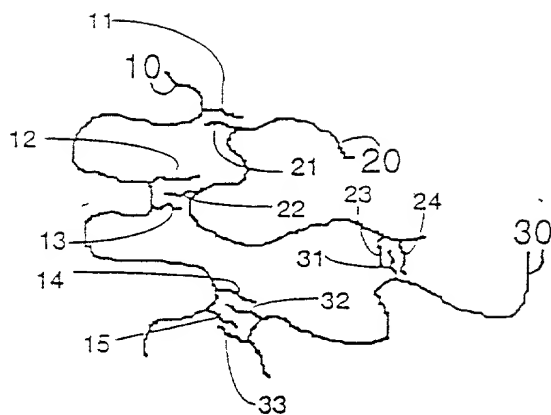


Figure 1

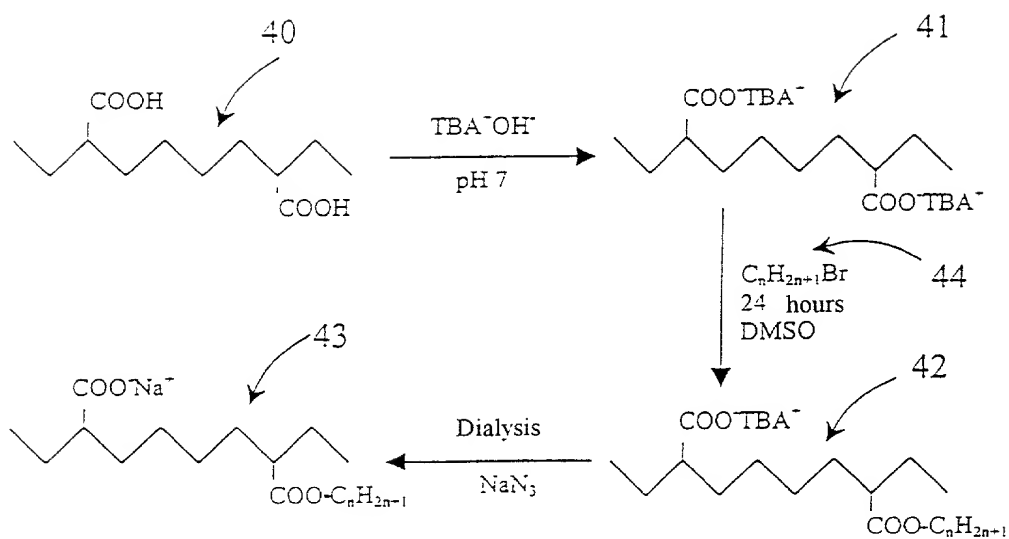
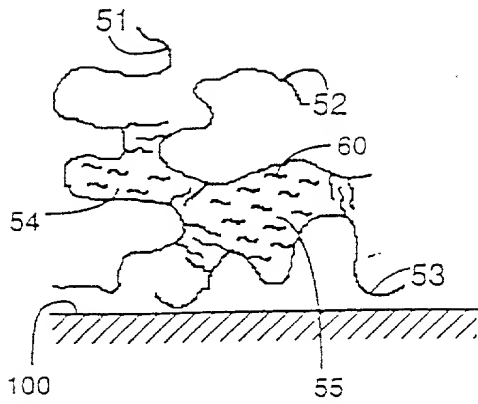
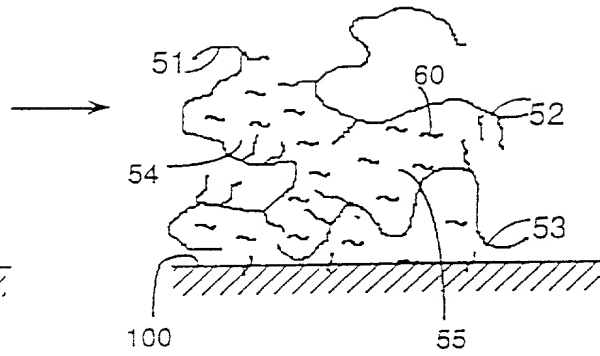
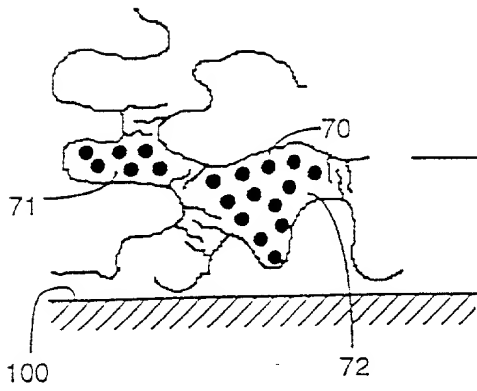
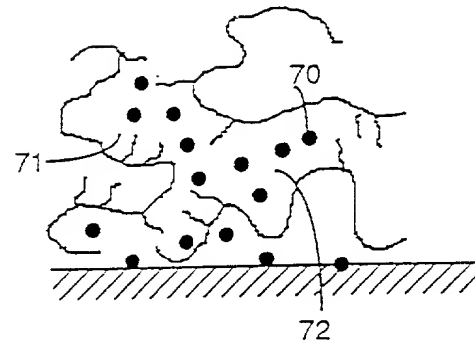


Figure 2

[illegible]



Figure 3Figure 4Figure 5Figure 6